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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,133	03/20/2001	Michael P. Vitek	5405.214	3028

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,133	VITEK, MICHAEL P.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that

require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. 101. This analysis should, of course, be tempered by consideration of the context and nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

See also the MPEP § 2107 - 2107.02.

Claims 1, and 3-10 are to a hemizygous transgenic mouse comprising an inactive endogenous inducible nitric oxide synthase (iNOS) gene and a transgene encoding a human iNOS gene wherein human iNOS production is not inducible by lipopolysaccharide (LPS) induction and a method of determining if a compound is capable of inducing Alzheimer's Disease (AD), Multiple Sclerosis (MS), Inflammatory Bowel Disease (IBD), and Rheumatoid Arthritis (RA) in the mouse of claim 1, and methods of screening a compound for activity in treating AD, MS, IBD, and RA in the mouse of claim 1.

The specification teaches a mouse comprising an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene (see pg. 3 lines 30-34 bridge pg. 3 lines 1-8).

However, at the time of filing, the skilled artisan would not have found utilities evident because the specification nor the art provide a phenotype for a mouse comprising an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene.

Thus the skilled artisan would not know how to use the claimed mouse or any results obtained from the claimed methods. Mice comprising an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene to determine if compounds of interest are capable of inducing or treating AD, MS, IBD, and RA lack specific utility because no correlation between a mouse comprising an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene and any disease or conditions are shown, and lack substantial utility because further research is required to determine a use for the results obtained.

The human iNOS gene is not disclosed as having a determined function or relation to any disease or condition, and symptoms ascribed to the mice comprising an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene are not specific to any disease or condition, the artisan at the time of filing would not know how to use the mice or any data resulting from using the mice to determine a treatment for any particular disease or condition. To make such a determination, the skilled artisan would need to further research the mice to determine those diseases and conditions associated with increased human iNOS production. This is additional evidence that the claimed invention lacks a specific or substantial utility.

As set forth in the utility guidelines summarized above, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a

disclosure of what condition can be diagnosed. Similarly, a statement of therapeutic utility for an unspecified disease is non-specific rendering the purported utility for the claimed mouse to be non-specific. As the methods are not disclosed to correlate to any specific disease, the methods lack a specific utility. The usefulness of the methods is not clear without assessing that they specifically correspond to a disease state, leaving the skilled artisan to speculate the utility of the methods of the claims. Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking a substantial utility. Presently, the skilled artisan would be required to further experiment to determine what diseases, if any, the claimed method would affect. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. The evidence of record has not provided any other utilities for the transgenic mouse encompassed by the claims that are specific and substantial.

In light of the above, the skilled artisan would not find the asserted utility of the mouse comprising an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene encompassed by the claims to be specific and substantial.

Claims 1, and 3-10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

Claims 1, and 3-10 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1, and 3-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a hemizygous transgenic mouse, wherein the mouse comprises an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene methods of using the mouse in screening potential compounds for induction and treatment of disease. However, the specification does not enable the claimed invention because at the time of filing the use of the claimed mouse and methods required undue experimentation without a predictable degree of success as explained below.

At the time of filing, the skilled artisan would not have regarded the claimed mouse or methods as having an enabled use. The mice are not disclosed by the specification as having any phenotype associated with a disease or condition associated with a human iNOS gene. The specification does not describe the mice as having any phenotype that would be due to an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene. Specifically, the specification has not shown that the claimed mice have any phenotype or linkage to the claimed methods involving AD, MS, IBD, and RA. Though the claimed mice have a human pattern of iNOS production in response to LPS stimulation, this demonstrates no enables use.

The specification teaches that mice comprising an inactive endogenous iNOS gene and a transgene encoding a human iNOS gene are "useful as models of inflammatory disease, including but not limited to Alzheimer's disease, Multiple Sclerosis, Inflammatory Bowel Disease and Rheumatoid Arthritis" (specification pg. 2 lines 23-25). The specification further

teaches that the generation of RA in the claimed mice is done by a "similar fashion" as mice that will be generated for MS "by injecting with myelin fractions to generate Experimental Allergic Encephalomyelitis (EAE) which is a model of Multiple Sclerosis in human" (specification pg. 4 lines 19-25). However, the art teaches that "in the mouse, a variety of strains are susceptible to EAE, and the myelin antigen used to induce disease varies with genotype at the major histocompatibility complex (MHC)" (Wong et al. pg. 99 col. 1 parag. 2 lines 2-6). The art continues to teach that in H-2^u mice the T-cell response is specific for myelin basic protein (MBP), in B10.PL mice EAE induction with Ac-11 typically leads to an acute disease course, and in I-A^u mice encephalitogenic T cells with specificity for Ac-11 vary little in t-cell receptor V-gene usage (Wong et al. pg. 9 col. 1 parag. 2 lines 7-13). The art teaches that NO and iNOS are involved in the development of MS, and that iNOS and nitrotyrosine has been detected in the tissue of the central nervous system of MS patients (Calabrese et al. pg. 581 col. 1 parag. 3 lines 1-12). The art continues to teach that "although evidence indicates that MS is a complex trait caused by interaction of genetic and environmental factors, little is known about its cause or the factors that contribute to it's unpredictable course" (Calabrese et al. pg. 580 col. 2 parag. 2 lines 1-5). However, the specification and the relevant prior art at the time of filing does not provide guidance for the induction of MS or RA. In fact, the causative agents or causative conditions for MS or RA had not yet been identified at the time of filing. Therefore, at the time of filing one skilled in the art would have had to engage in an undue amount of experimentation to use the claimed mouse and methods involving RA and MS without a predictable degree of success.

With regard to AD development in the claimed mice the specification teaches that "using primed human monocyte derived macrophages as models of microglia, apolipoprotein-E (ApoE)

can stimulate nitric oxide (NO) production" (specification pg. 5 lines 14-17). However, the art teaches that NO production in cultured human monocyte-derived macrophages is not stimulated by ApoE alone, and is only stimulated when ApoE is used in conjunction with polyinosinic:polycytidylic acid or amyloid beta peptides (Vitek et al. pg. 392 col. 2 lines 1-15 and figs. 1-3). Further, the art teaches that this stimulation of NO is done under *in vitro* conditions and has not been demonstrated in an *in vivo* model that would characterize Alzheimer's development (Vitek et al. pg. 392 col. 1 parag. 2). At the time of filing the art teaches "that all three isoforms of nitric oxide synthase (NOS) are upregulated in brains of AD cases" (Luth et al. pg. 140 col. 1 lines 4-6), and that "expression of iNOS and eNOS is increased both in neurons and in glial cells in AD compared to control" (Luth et al. pg. 140 col.1 lines 9-11). Further, the art teaches that "it is still a matter of debate which AD specific signals are responsible for the increased levels of all three NOS isoforms in the AD brain" (Luth et al. pg. 141 cols. 1-2 parag. lines 1-3). However, the specification and the relevant prior art at the time of filing does not provide guidance for the induction of AD. In fact, the causative agents or causative conditions for AD had not yet been identified at the time of filing.

Therefore, at the time of filing one skilled in the art would have had to engage in an undue amount of experimentation to use the claimed mouse and methods involving AD without a predictable degree of success.

With regard to IBD, the specification gives no guidance to how IBD would be induced in the claimed mouse or how to use the claimed methods to determine if a compound is capable of inducing or treating IBD. However, at the time of filing, the art teaches that transgenic mouse models involving iNOS gene deletion vary significantly in the development of experimental

colitis which is a model of IBD (Kolios et al. pg. 432 col. 2 parag. 4 lines 1-12 bridge pg. 433 col. 1 parags. 1-3 and table 2). The art continues to teach that in patients with ulcerative colitis, the most common form of IBD, iNOS activity is significantly increased in the colonic mucosa compared to control patients (Kolios et al. pg. 430 col. 1 parag. 1 lines 16-17), and that the up-regulation of iNOS has been shown to correlate well with prolonged colonic inflammation (Kolios et al. pg. 431 col. 1 parag. 2 lines 5-7). At the time of filing the art does not teach how the claimed "humanized" mouse with a human pattern of iNOS expression would be able to be used to model the human development of IBD. However, the specification and the relevant prior art at the time of filing does not provide guidance for the induction of IBD. In fact, the causative agents or causative conditions for IBD had not yet been identified at the time of filing (Kolios et al. pg. 430 col. 2 parag. 3 lines 7-11).

Therefore, at the time of filing one skilled in the art would have had to engage in an undue amount of experimentation to use the claimed mouse and methods involving AD, MS, RA, and IBD without a predictable degree of success.

Therefore, the skilled artisan would have been required to engage in an undue amount of experimentation at the time of filing to implement the invention as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari, Ph.D whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

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